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Nickel-Catalyzed Asymmetric Ullmann Coupling for the Synthesis of Axially Chiral Tetra-ortho-Substituted Biaryl Dials

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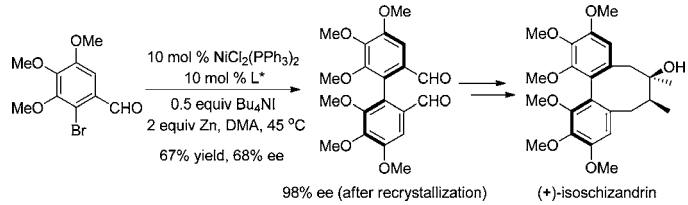
ABSTRACT



The first example of nickel-catalyzed asymmetric Ullmann coupling of bis-ortho-substituted arylhalides is described. With the chiral BINOL-based monodentate phosphoramidite ligand, the reaction allows atropoenantioselective synthesis of a series of axially chiral tetra-ortho-substituted biaryl dials. By taking advantage on this asymmetric Ullman coupling as a key stereogenic axis-forming reaction, the formal synthesis of (+)-isoschizandrin was accomplished.

Axially chiral biaryls are common scaffolds in a large number of natural products and biologically active molecules.[1] They have also been widely used as powerful chiral ligands or auxiliaries in asymmetric synthesis.[2] Due to their great importance, considerable efforts have been devoted in recent decades to developing methods for efficiently constructing axial chirality.[3] Axially chiral biaryl dials with two *o*-carbaldehyde functionalities represent a promising class of compounds, they are extremely useful precursors to a range of important biaryl compounds.[4] In spite of a few reports regarding asymmetric synthesis of optically active biaryl dicarboxylic acids,[5] nonresolution,[6] straightforward synthetic routes to axially chiral biaryl dials relying on a chiral catalyst-

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(3) For recent reviews, see: (a) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193. (b) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (c) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197. (d) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223. (e) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (f) Bringmann, G.; Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615. (g) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (h) Kamikawa, K.; Uemura, M. *Synlett* **2000**, 938. (i) Cepanec, I. *Synthesis of Biaryls*; Elsevier: New York, 2004, pp 293−320.

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promoted asymmetric strategy such as oxidative coupling[7] or Ullmann coupling[8] remain significantly undeveloped.[9] In this paper, we describe the results of our investigations on direct construction of a series of axially chiral tetra-ortho-substituted biaryl dials via the nickel-catalyzed asymmetric Ullmann coupling approach using monodentate phosphoramidite as chiral ligand. To our knowledge, this is the first example of catalytic atropoenantioselective Ullmann coupling.

Since its discovery in 1901, the Ullmann reaction has been recognized as one of the most powerful and common methods for the synthesis of biaryl compounds.[10] Various Ullmann-type coupling procedures have been developed through the last century; however, few are suitable for the atropselective synthesis of axially chiral biaryls due to the difficulty in controlling the axial chirality. Successful examples, without exception, involved the use of chiral substrates as the starting point.[11] A catalytic asymmetric strategy for biaryl axis control is in high demand. In an earlier work, we reported the development of a nickel-catalyzed Ullmann-type reaction to prepare tetra-ortho-substituted biaryls.[12] Notably, the $NiCl_2(PPh_3)_2$/Zn catalyst system was able to promote the homocoupling of highly sterically hindered substrates under relatively mild conditions in the presence of Bu_4NI. We thus envisioned that the use of a chiral nickel catalyst might benefit the reaction axial stereocontrol, leading to the formation of axially chiral biaryls.

Scheme 1. Initial Attempts with Chiral Phosphoramidite Ligands

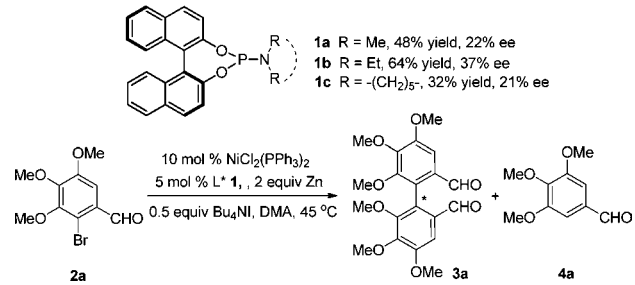
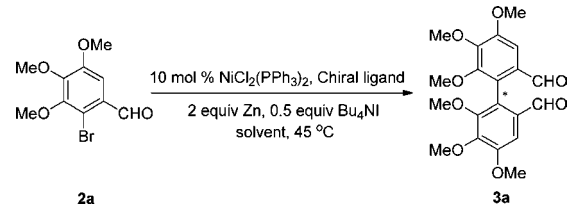


Table 1. Conditions Optimization and Ligand Screening[a]



entry	ligand	solvent	time (h)	convn (%)	yield (%)[b]	ee (%)[c]
1	**1b**	DMA	4	100	64	37
2[d]	**1b**	DMA	4	100	54	36
3[e]	**1b**	DMA	11	100	40	28
4	**1b**	toluene	24	30	8	35
5	**1b**	dioxane	7	49	10	40
6	**1b**	THF	6	100	25	33
7	**1b**	DMF	9	78	10	37
8	**1b**	NMP	5	71	25	39
9	**1b**	HMPA	5	60	61	23
10[f]	**1b**	DMA	12	83	44	44
11	**1d**	DMA	3	100	56	59
12[d]	**1d**	DMA	3	100	67	68
13[d]	**1e**	DMA	3	100	67	66
14[d]	**1f**	DMA	3	100	62	58
15[d]	**1g**	DMA	3	100	59	60

[a] Reactions were carried out on a 0.2 mmol scale under Ar with 0.1 equiv of catalyst, 0.05 equiv of chiral ligand, 2 equiv of activated Zn, and 0.5 equiv of Bu_4NI at 45 °C, unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC on a Chiral Pak AD-H column. [d] 0.1 equiv of chiral ligand. [e] 0.2 equiv of chiral ligand.; [f] Room temperature.

To test the feasibility of the above consideration, we sought to apply chiral BINOL-based monodentate phosphoramidite ligand to the nickel-catalyzed Ullman coupling of 2-bromo-3,4,5-trimethoxybenzaldehyde **2a**. The preliminary experiments were performed in DMA (*N*,*N*-dimethylacetamide) at 45 °C with $NiCl_2(PPh_3)_2$/Zn/Bu_4NI in the presence of ligands **1a**−**c** (Scheme 1). Very gratifyingly, the desired product biaryl dial **3a** with significant ee values in all cases was observed, giving a promising 37% ee when (*S*)-Et-monophos

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(5) (a) Seki, M.; Yamada, S.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **2000**, 1677. (b) Furutani, T.; Hatsuda, M.; Imashiro, R.; Seki, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4763. (c) Andrus, M. B.; Asgari, D.; Sclafani, J. A. *J. Org. Chem.* **1997**, *62*, 9365. (d) Oi, S.; Matsuzaka, Y.; Yamashita, J.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 956. (e) Kanoh, S.; Hongoh, Y.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1032.

(6) For two known kinetic resolution reports, see: Annunziata, R.; Benaglia, M.; Raimondi, L. *Tetrahedron* **2001**, *57*, 10357, and ref 5a.

(7) For two examples of biaryl dial synthesis via chiral substrate-induced asymmetric oxidative coupling, see: (a) Neo, A. G.; Gref, A.; Riant, O. *Chem. Commun.* **1998**, 2353. (b) Larsen, A. O.; Taylor, R. A.; White, P. S.; Gagné, M. R. *Organometallics* **1999**, *18*, 5157.

(8) For two examples of biaryl dial synthesis via chiral substrate-induced asymmetric Ullmann coupling, see: (a) Patti, A.; Lambusta, D.; Piattelli, M.; Nicolosi, G. *Tetrahedron: Asymmetry* **1998**, *9*, 3073. (b) Stavrakov, G.; Keller, M.; Breit, B. *Eur. J. Org. Chem.* **2007**, 5726.

(9) For an intramolecular approach utilizing chiral carbon−carbon bridges to nonracemic biaryl dialdehyde synthesis, see: Bringmann, G.; Keller, P. A.; Rölfing, K. *Synlett* **1994**, 423.

(10) (a) Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174. (b) Ullmann, F.; Meyer, G. M.; Loewenthal, O.; Gilli, E. *Liebigs Ann. Chem.* **1904**, *332*, 38. For recent reviews, see: (c) Nelson, T. D.; Crouch, R. D. *Org. React. (N.Y.)* **2004**, *63*, 265–555. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096.

(11) For selected examples of substrate-induced asymmetric Ullmann coupling, see: (a) Miyano, S.; Tobina, M.; Nawa, M.; Sato, S.; Hashimoto, H. *J. Chem. Soc., Chem. Commun* **1980**, *24*, 1233. (b) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2655. (c) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991. (d) Rawal, V. H.; Florjancic, A. S.; Singh, S. P. *Tetrahedron Lett.* **1994**, *35*, 8985. (e) Lipshutz, B. H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc.* **1991**, *113*, 8161. (f) Lipshutz, B. H.; Siegmann, K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9296. (g) Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. *Angew. Chem., Int. Ed.* **1994**, *33*, 1842. (h) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1999**, *121*, 2762, and ref 4c.

(12) Hong, R.; Hoen, R.; Zhang, J.; Lin, G.-Q. *Synlett* **2001**, 1527.

1b was employed as the ligand. Like coupling reactions in the previously reported system,[12] the reductive product **4a** was also inevitably formed in considerable amounts in the current mild system.

Encouraged by the results obtained, we next investigated the reaction variables. It seems that a proper Ni/ligand ratio is very important. When the chiral ligand loading of **1b** was increased to 20 mol %, both the yield and ee dropped dramatically (Table 1, entries 1−3). The use of DMA as solvent provided better results in terms of reaction conversion, yield, and enantioselectivity (entries 4−9). When the reaction was carried out at room temperature, a slightly better enantioselectivity (44%) could be obtained; however, the yield is not ideal due to the incomplete conversion even after prolonged stirring (entry 10).

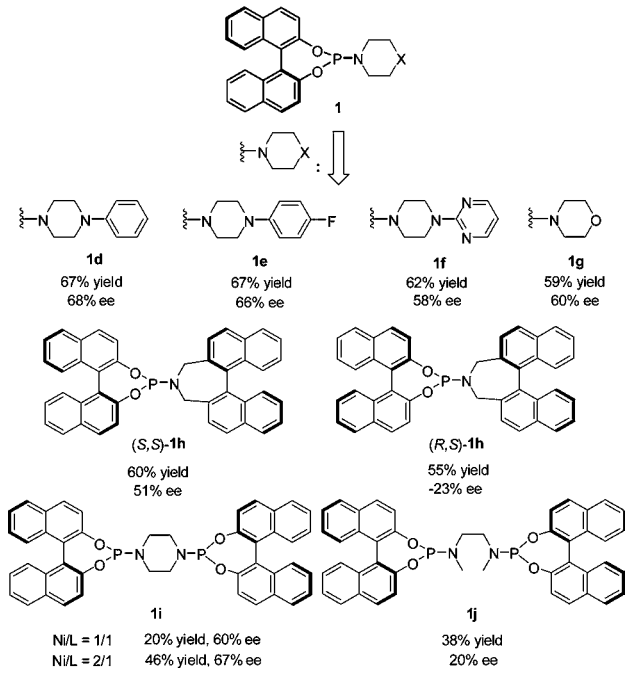
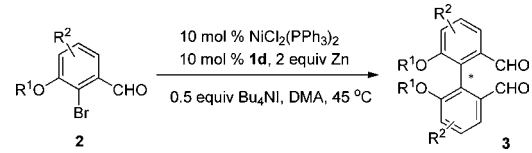


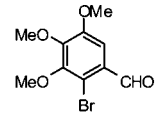
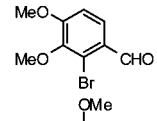
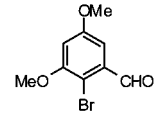
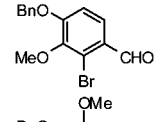
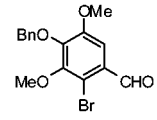
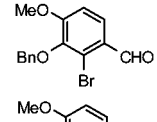
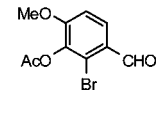
Figure 1. Selected phosphoramidite ligands for asymmetric Ullmann coupling.

To attain higher atropselectivity of the resulting biaryl dial **3a**, a variety of chiral BINOL-based phosphoramidite ligands were prepared[13] and examined in the nickel-catalyzed asymmetric Ullman coupling of **2a**. Some selected results are summarized in Table 1 and Figure 1. We were pleased to find that monodentate phosphoramidites **1d**, **1e**, **1f**, and **1g** with a heterocyclic piperazine or morpholine substitution on the phosphorus were more effective ligands. By lowering the Ni/Ligand ratio to 1:1, these Ni-complexes all showed enhanced catalyst activities, providing the corresponding biaryl dial **3a** with up to 68% ee in moderate yields (entries 11−15). But attempts to further improve ee by using ligands (*S*,*S*)- and (*R*,*S*)-**1h** containing an extra chiral BINOL-based amino scaffold were not successful (Figure 1). Other types of phosphoramidite ligands including bidentate **1i** and **1j** did not give better results either. It is worth noting that utilizing bidentate phosphorus ligands such as BINAP will afford the undesired phthalide.[14]

Subsequently, the catalyst Ni/**1d** system was applied to the asymmetric Ullman coupling of a range of bis-ortho-substituted arylhalides having an aldehyde functionality (Table 2). As shown in entries 1−5, substrates with substitution variations at the meta- and para-positions of the benzene ring all gave the expected biaryl dial products, and in most cases nearly comparable yields and enantioselectivities were obtained. When one *o*-methoxy group was replaced by a sterically more hindered benzyloxy, the reaction still proceeded well, but no great improvement on enantio-control was observed (60% ee, entry 6). In addition, a significant ee drop was found when changing the *o*-alkoxy to carbonyl containing acetoxy (entry 7), suggesting the coordination pattern difference in the reaction transition state.

Table 2. Nickel-Catalyzed Asymmetric Ullmann Coupling[a]



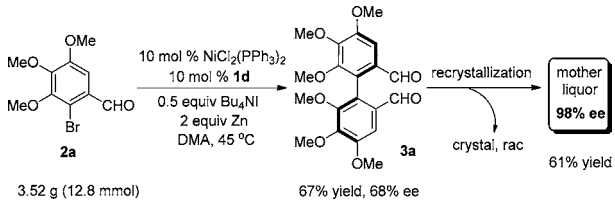
entry	substrate	product	time (h)	yield (%)[b]	ee (%)[c]
1		**3a**	3	67	68
2		**3b**	3	55	58
3		**3c**	5	65	44
4		**3d**	6	62	61
5		**3e**	6	60	58
6		**3f**	6	62	58
7[d]		**3g**	8	31	15

[a] Reactions were carried out on a 0.2 mmol scale in DMA (0.5 mL) under Ar at 45 °C. [b] Isolated yield. [c] Determined by HPLC on a Chiral Pak AD-H column. [d] 60 °C.

(13) For related reference procedures, see: (a) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865. (b) Bernsmann, H.; Van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; De Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943. (c) Eberhardt, L.; Armspach, D.; Matt, D.; Toupet, L.; Oswald, B. *Eur. J. Org. Chem.* **2007**, 5395. (d) Reetz, M. T.; Mehler, G.; Bondarev, O. *Chem. Commun.* **2006**, *21*, 2292.

Interestingly, during the ee determination of the product **3a**, we observed an unusual heterochiral crystallization phenomenon similar as we reported for chiral 3-arylphthalide compounds.[14b,15] In the recrystallization process, the formation of heterochiral crystal (racemic) is much more preferential than that of homochiral crystal (enantiomorphous). As a result, using the initial compound with 68% ee to start, highly enantiomerically enriched **3a** (98% ee) in mother liquor was readily afforded through rapid crystallization. Notably, the coupling reaction of **2a** could be conducted on grams scale with catalytic amounts of Ni/**1d** and maintain the same levels of both enantioselectivity and yield. After recrystallization, biaryl dial (*R*)-**3a**[16] with 98% ee can be easily accessed in 61% yield (Scheme 2).

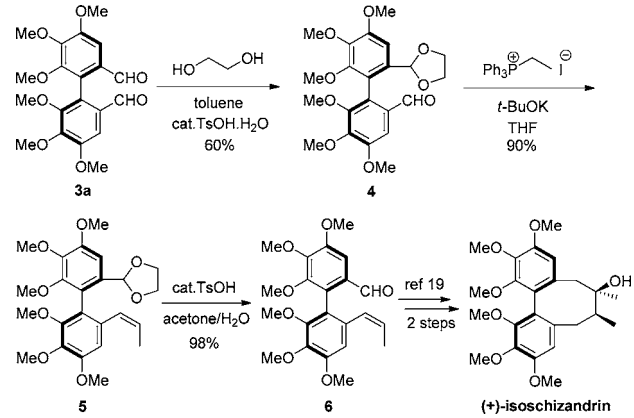
Scheme 2. Access to Enantioenriched **3a**



Having successfully set the biaryl stereochemistry, we sought to demonstrate its synthetic utility. Dibenzocyclooctadiene type lignan (+)-isoschizandrin isolated from chinese *Schisandra chinensis*[17] attracted our interest because of its unique axially chiral biaryl structure. The stereoselective total synthesis of (+)-isoschizandrin has been previously achieved by two research groups.[18,19] In Molander's synthetic approach,[19] the enantiomerically enriched unsaturated aldehyde (*R*)-**6** was prepared in 9 steps from the racemic biaryl dial **3a**, using the kinetic resolution strategy. In our hands, starting from axially chiral biaryl dial (*R*)-**3a** (98% ee), monoprotected (*R*)-**4** could be readily obtained, and was then smoothly converted into the key intermediate (*R*)-**6** via a two-step Wittig reaction/hydrolysis sequence (Scheme 3). Notably, the olefin *Z*/*E* selectivity around 6:1 was obtained in the Wittig reaction.[20] Utilizing Molander's specific SmI_2-promoted 8-endo ketyl-olefin cyclization approach,[19] (+)-isoschizandrin could be stereoselectively constructed finally in 2 steps. Accordingly, our formal synthesis represents the most expedient route to (+)-isoschizandrin reported to date.

In summary, we have developed an unprecedented nickel-catalyzed asymmetric Ullmann coupling of bis-ortho-substituted arylhalides. With chiral BINOL-based monodentate phosphoramidite ligands, the reaction allows atropoenantioselective synthesis of a series of axially chiral tetra-ortho-substituted biaryl dials. The asymmetric catalysis followed by efficient heterochiral crystallization provides a very convenient access to highly enantiomerically enriched biaryl dial **3a**. Furthermore, the formal synthesis of (+)-isoschizandrin was accomplished by taking advantage on the nickel-catalyzed asymmetric Ullman coupling reaction as key stereogenic axis-forming transformation. We believe that the current study offers a promising example for future asymmetric Ullman reactions design.

Scheme 3. An Efficient Formal Synthesis of (+)-Isoschizandrin



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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR, HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Lei, J.-G.; Hong, R.; Yuan, S.-G.; Lin, G.-Q. *Synlett* **2002**, 927. (b) Chen, W.-W.; Xu, M.-H.; Lin, G.-Q. *Tetrahedron Lett.* **2007**, *48*, 7508.

(15) For other biaryl (BINOLs) examples of observation of more favorable crystallization of the racemate, see: Li, X.; Hewgley, B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500. For a related general discussion, see: Walsh, P.; Kowzlowski, M. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, CA, 2008; Chapter 11.

(16) The absolute configuration was assigned as (*R*) by comparison of optical rotation value with that reported in refs 4a and 4c.

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(18) (a) Tanaka, M.; Itoh, H.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Tetrahedron: Asymmetry* **1993**, *4*, 605. (b) Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *J. Org. Chem.* **1995**, *60*, 4339.

(19) Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533.

(20) In Molander's work, TIPS ether at 2-position instead of dioxolane was used, and a 4:1 *Z*/*E* ratio was obtained.